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Consecutive dynamic resolutions of phosphine oxides†

Felix A. Kortmann,[a] Mu-Chieh Chang,[a] Edwin Otten,[a] Erik P. A. Couzijn,*[b] Martin Lutz[c] and Adriaan J. Minnaard*[a]

A crystallization-induced asymmetric transformation (CIAT) involving a radical-mediated racemization provides access to enantiopure secondary phosphine oxides. A consecutive CIAT is used to prepare enantio- and diastereo-pure *tert*-butyl(hydroxyalkyl)phenylphosphine oxides.

Introduction

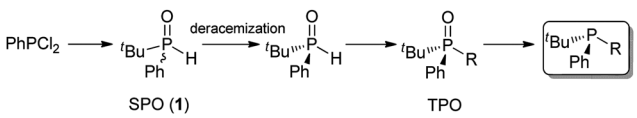
Phosphine oxides play an important role as precursors for chiral phosphine ligands as well as being powerful ligands themselves.[1,2] Recently, bisphosphine monoxides have caught considerable attention due to their hemilabile coordination.[3] While asymmetric catalysis with phosphine–transition metal complexes initially employed ligands that were stereogenic at phosphorus (P-chiral ligands, such as monodentate CAMP and its dimer DiPAMP), ligands with backbone chirality turned out to be more readily accessible and emerged subsequently in numerous variations (*e.g.* DIOP, BINAP, JOSIPHOS).[4–6] Currently, however, the use of P-chirality faces a remarkable revival as illustrated by the advent of catalysts based on, for example, the BIBOP,[7] SMS-Phos,[8] and Tangphos[9] ligands. The enantioselectivity and turnover frequency of these catalysts in some cases surpass those reached by catalysts based on backbone-chiral ligands.[10–12]

The synthetic accessibility of enantiopure P-chiral compounds is a fundamental challenge and some of the pursued approaches are important contributions to organic chemistry. The first methods to be developed for resolution relied on diastereomeric complex formation or a covalently attached chiral auxiliary. In particular, the use of menthol phosphinates has broad scope.[13,14] Asymmetric synthesis has been studied intensively as well,[15,16] and two methods stand out: the Jugé–Stephan method based on the addition of organolithium reagents to *N*-ephedrinophosphine-P-borane, an approach that very recently has been extended by a research group of Boehringer Ingelheim,[17] and the BuLi/spartein-mediated desymmetrization of aryldimethylphosphine-P-borane.[18,19] The latter has been extended to a dynamic thermodynamic resolution variant.[20] Both methods are frequently applied but scale-up is not always straightforward since purification by chromatography is often involved.

Phosphine oxides, both secondary (SPO) and tertiary (TPO), seem to be for us the ideal precursors to enantiopure tertiary phosphines. Phosphine oxides are readily prepared on the large scale in racemic form, are air- and moisture-stable and most often crystalline. The reduction of tertiary phosphine oxides without racemization is now well established.[21–26] It is therefore not surprising that a lot of P-chiral phosphines are prepared *via* their phosphine oxides and subsequent reduction.[2,27] Unfortunately, the bottleneck is the access to enantiopure phosphine oxides, currently obtained *via* resolution. Obviously, this is accompanied by the disadvantages of a diastereomeric separation.

We realized that this situation would strongly improve upon replacement of the resolution with a deracemization of a secondary phosphine oxide followed by a stereoselective conversion into the tertiary phosphine oxide and subsequent reduction (Scheme 1), here exemplified by starting from $PhPCl_2$.

The choice to prepare racemic secondary phosphine oxides assures straightforward availability of the starting material and gives full freedom in the introduction of the third substituent.[10,15,16,28] Alkylation, arylation,[29–32] alkene addition,[33] and conjugate addition[34] of secondary phosphine oxides have all been well described and take place without erosion of enantiopurity. The missing piece in this scheme is the



Scheme 1 A synthetic route towards enantiopure P-chiral *tert*-butylphenylphosphines.

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deracemization of the secondary phosphine oxide and, surprisingly, this has not been reported.

We report here the crystallization-induced deracemization of secondary phosphine oxides and provide solid evidence that this is a radical-mediated process. A consecutive novel crystallization-induced asymmetric transformation (CIAT) provides access to enantio- and diastereo-pure *tert*-butyl(hydroxyalkyl)-phenylphosphine oxides (Scheme 2).

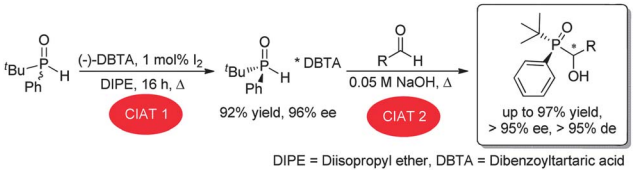
Results and discussion

Our study is based on *tert*-butylphenylphosphine oxide **1**, the most used secondary phosphine oxide in catalysis, which is prepared from dichlorophenylphosphine and *tert*-butylmagnesium chloride in 96% yield. Recently, we reported an efficient resolution for **1** using dibenzoyltartaric acid.[35] In contrast to suggestions in the literature,[36] **1** proved to be configurationally very stable. Racemization attempts under Brønsted/Lewis acidic or strongly basic conditions were unsuccessful, except for heating in concentrated hydrochloric acid, which led to racemization but also to degradation (see ESI for details†).

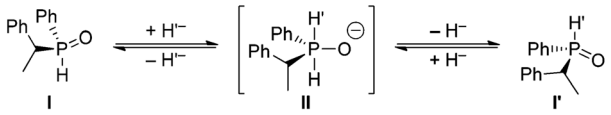
Inspired by work of Mislow *et al.*[37] comprising a hydride-induced epimerization (Scheme 3), we observed that **1** does racemize with $LiAlH_4$, too. This mechanism proceeds by hydride addition–elimination *via* an achiral pentacoordinate dihydrido species **II**.

As $LiAlH_4$ was not compatible with our resolution and in addition led to partial reduction of **1**, other strong nucleophiles (4,5-dicyanoimidazole, imidazolium triflate) were studied that might generate a pentacoordinate intermediate, stereomutation of which would eventually lead to racemization.[38–40] All attempts failed, however, until an example of an iodine-catalyzed diastereomeric resolution by Vedejs and Donde for a tertiary *phosphine* was taken into consideration.[41] To our great delight, **1** racemized by heating with only catalytic amounts of iodine.

This racemization protocol was at least in principle compatible with our resolution *via* diastereomeric complex formation. After extensive optimization, the combination of 1% iodine and stoichiometric (−)-L-dibenzoyltartaric acid (DBTA) as the resolving agent in refluxing diisopropyl ether, followed by hot filtration of the crystalline mass, provided the complex in an excellent 92% yield and 96% ee (Scheme 4). After recrystallization from toluene/diisopropyl ether the SPO was obtained as a single enantiomer. The free phosphine oxide **1** is readily obtained from the complex in quantitative yield by washing with aqueous base. Thus, *via* an unprecedented and readily



Scheme 2 Crystallization-induced asymmetric transformations.



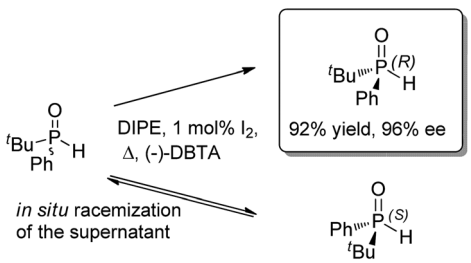
Scheme 3 $LiAlH_4$-induced epimerization as described by Mislow *et al.*

scalable crystallization-induced dynamic resolution (deracemization)[42] the secondary phosphine oxide **1** can be obtained in excellent yield and ee. As both enantiomers of DBTA are commercially available, both enantiomers of **1** are accessible.

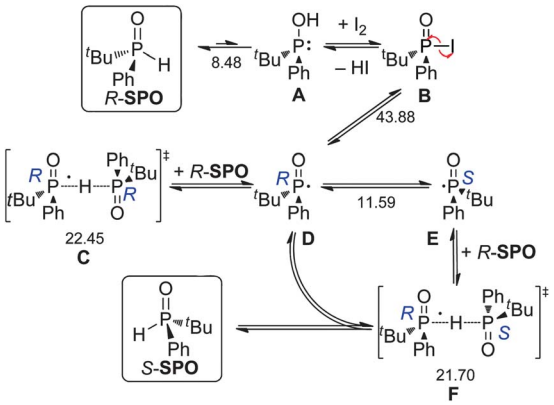
An often undervalued characteristic of crystallization-induced dynamic resolutions, based on *thermodynamic* product formation, is that the efficiency of the underlying resolution is less important, in contrast to dynamic *kinetic* resolutions. Even a small solubility difference for the two crystalline diastereomeric complexes should lead to an effective deracemization as the equilibrium in solution is shifted to the less soluble diastereomer. To illustrate this principle we carried out the dynamic resolution with (*S*)-BINOL as the resolving agent. BINOL is known to form diastereomeric complexes with **1**, but the solubility difference is insufficient for an effective resolution.[43] Applied in the crystallization-induced dynamic resolution, however, BINOL provided a rewarding 81% yield and 91% ee.[44] Provided that diastereomeric complexes are formed with a given secondary phosphine oxide using either DBTA or another agent, this CIAT will produce highly enantioenriched products that can be easily recrystallized to yield a single enantiomer. We did not attempt to expand the method in this way, as the third substituent in the tertiary phosphine can be freely chosen (*vide supra*) in this strategy. This provides already considerable scope.

Iodine is known to readily convert **1** into its corresponding phosphinyl iodide **B**[45] and HI (Scheme 5), as was confirmed by the observation of **B** by NMR spectroscopy (see ESI†), an increase in acidity, and bleaching of the solution within minutes. We distrusted, however, racemization mechanisms in which the formed iodide acts as a nucleophile, as has been reported for phosphine epimerization. Other strong nucleophiles were not able to bring about racemization and also iodide added in the form of *n*-Bu_4NI had no influence on the reaction. Moreover, all attempts to detect pentavalent phosphorus species, intermediates in such a racemization mechanism, by NMR spectroscopy failed.

Therefore, Density-Functional Theory (DFT) calculations were performed using Gaussian 09;[47] see the ESI for details.†



Scheme 4 SPO synthesis *via* CIAT **1**.



Scheme 5 Radical mechanism for racemization of **1** with calculated Gibbs free energy barriers at 343 K in kcal mol^{-1}.

Structures were fully optimized at the B3LYP/6-31G(d),I:LanL2DZ(d) level of theory with the SMD solvation model[46] for diisopropyl ether (DIPE). Frequency analyses afforded Gibbs free energy corrections at 70 °C, which were combined with B3LYP/6-311+G(2d,p),:6-311G(2d)/SMD(DIPE) single-point energies to determine the reaction energetics.

We initially considered SPO racemization to occur through the stereomutation[38–40] of pentacoordinate phosphorane intermediates. However, none of the possible stereoisomeric adducts of SPO with HI, I$^-$, or I$^\bullet$ could be located at the used level of theory. Instead, the optimized structures corresponded to (^{t}Bu)(Ph)PH(OH)$^+$ (for HI) or SPO having a weak interaction with I$^-$ or I$^\bullet$, respectively. Thus, a stereomutational mechanism can be excluded.

We were triggered, though, by the observed erosion of enantiopurity by Han and Zhao[33] in the radical addition of secondary phosphine oxides to alkenes, and in their oxidative dimerization by Haynes *et al.*[48] Our DFT calculations indicate that the P–I bond in **B** is weak (43.88 kcal mol^{-1} at the used level of theory) and can be cleaved, providing a phosphinyl radical **D**,[49,50] which was indeed detected by trapping experiments with norbornadiene and 3,4-dihydro-2-*H*-pyran.[51] The racemization barrier of **D** was calculated to be only 11.59 kcal mol^{-1}, whereas the barriers for hydrogen transfer between **1** and **D** with either opposite or the same absolute stereochemistry (21.70 and 22.45 kcal mol^{-1}, respectively) are also surmountable at 70 °C. Taken together, this establishes a very effective racemization mechanism *via* a radical chain process that explains all observations in this study.

Remarkably, the use of a radical-mediated racemization in a dynamic resolution has very limited precedent.[52] Both the synthesis of the racemate and the dynamic resolution scale readily, and do not require low-temperature conditions or chromatography. Combined with the well worked-out conversion of the product to enantiopure phosphines, this provides an approach that is comparable in efficiency to the recently disclosed Boehringer Ingelheim procedure.[17c]

With enantiopure **1** in hand, its addition to aldehydes was studied in order to transfer chirality to carbon and obtain straightforward access to *tert*-butyl(hydroxyalkyl)phenylphosphine oxides (Scheme 6).

This reaction has been reported with aromatic aldehydes applying a stoichiometric amount of a strong base (LDA).[34] We realized that viewing hydroxy phosphine oxides as phosphabenzoins, this would imply that catalytic base should be sufficient and moreover that the reaction should be reversible. Given the observation that the addition products are invariably crystalline solids, this provoked the development of a second crystallization-induced dynamic resolution.

Upon exposure of an equimolar mixture of **1** and benzaldehyde to 0.05 M aq. sodium hydroxide, the corresponding *tert*-butyl(hydroxybenzyl)phenylphosphine oxide was formed within minutes as a white precipitate consisting of a nearly 1 : 1 mixture of diastereomers. When this suspension was heated to 80 °C, dynamic resolution occurred readily to afford a single diastereomer in 89% isolated yield (Scheme 7).

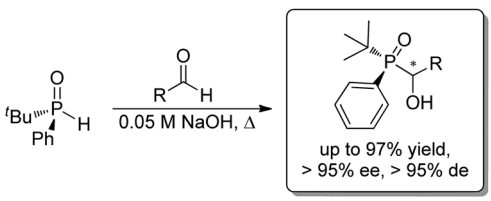
The reaction turned out to have a remarkably broad scope, both aromatic and enolizable aliphatic aldehydes[53] being suitable substrates. For the latter there is a preference for one diastereomer already at room temperature, and a single reprecipitation afforded the diastereomerically pure products. The quantitative addition to formaldehyde (Table 1, entry 11) afforded enantiopure *tert*-butyl(hydroxymethyl)phenylphosphine oxide, which until now was only accessible *via* enzymatic resolution.[54]

For electron-poor aromatic aldehydes, above 50 °C a phospha-Brook rearrangement to the corresponding benzyl phosphinate occurred as a competing reaction (Scheme 8).[55] Therefore diastereomerically pure products could be obtained at 80 °C, but only in low yields.

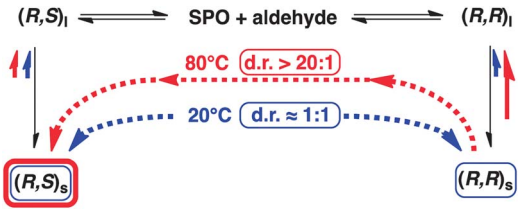
The stereochemistry of the newly formed stereocenter was established by ^{1}H NMR spectroscopy using the method of Verkade, relating $^2J_{P,H}$ to the relative stereochemistry.[56] As shown before (*vide supra*, see ESI†) the P stereocenter is configurationally stable under the applied reaction conditions. This determination was underpinned by X-ray crystallography (Scheme 9).

As in the first dynamic resolution, the stereochemical outcome of the second CIAT is solely determined by the product solubilities and the configuration of the starting SPO; *e.g.* the asymmetric transformation of (*R*)-**1** and (*S*)-**1** with benzaldehyde affords only the *R*,*R*- and *S*,*S*-stereoisomers, respectively, and not their diastereomers. We were therefore delighted to observe that the corresponding reaction of (*R*)-**1** and (*S*)-**1** with *p*-tolualdehyde afforded the *R*,*S*- and *S*,*R*-stereoisomers. As in the well-known quinine–quinidine example,[58] **2** and **3** can be regarded as quasi-diastereomers.

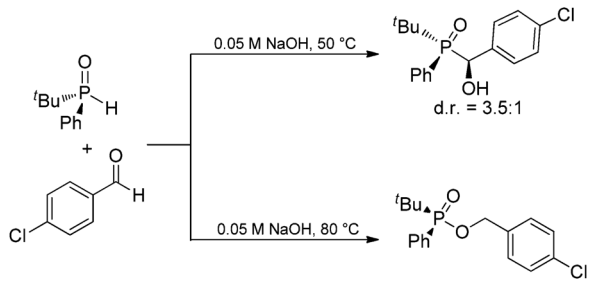
This again points at the important characteristic of dynamic resolutions based on thermodynamic product formation: the



Scheme 6 TPO synthesis *via* CIAT **2**.

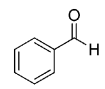
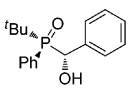
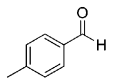
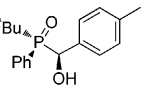
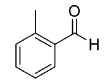
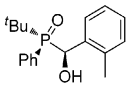
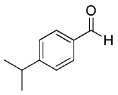
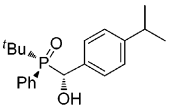
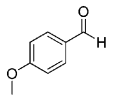
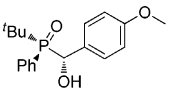
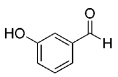
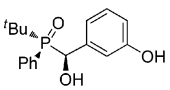
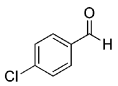
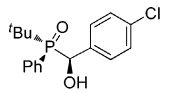
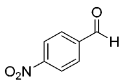
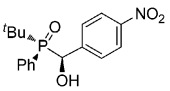
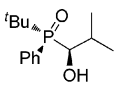
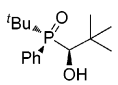
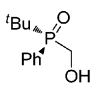
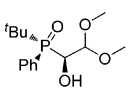


Scheme 7 CIAT 2.

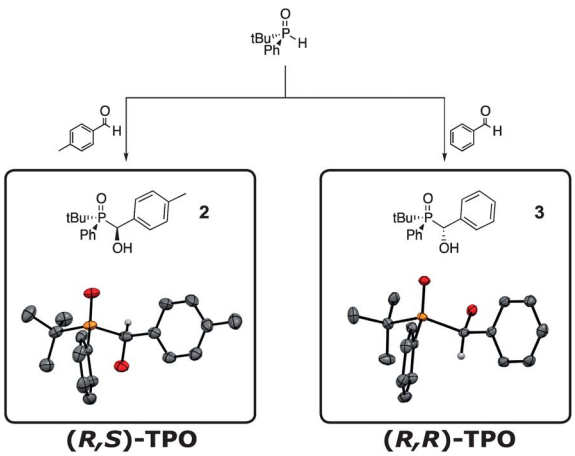


Scheme 8 Reaction outcome of *tert*-butyl(hydroxyalkyl)phenylphosphine oxide synthesis for electron-poor aldehydes.

Table 1 Substrate scope of *tert*-butyl(hydroxyalkyl)phenylphosphine oxide synthesis *via* CIAT 2

Entry	Substrate	Product	d.r.[a]	Yield (%)
1			>20 : 1 (R_p,R)	89
2			>1 : 20 (R_p,S)	94
3			>1 : 20 (R_p,S)	94
4			>20 : 1 (R_p,R)	96
5			>20 : 1 (R_p,R)	96
6			1 : 20 (R_p,S)	90
7			1 : 3.5[b]	90[b]
8			1 : 4.4[b]	93[b]
9			>1 : 20[c] (R_p,S)	95[c]
10			>1 : 20[c] (R_p,S)	89[c]
11			n.a.	Quant.
12			>1 : 20	56

[a] Determined by ^{1}H and ^{31}P NMR spectroscopy. [b] Reaction conducted at 50 °C; at higher temperatures the product rearranges to the corresponding phosphinate. [c] Reaction conducted at 20 °C and product reprecipitated once from MeOH/H_2O.



Scheme 9 Formation of pseudo-diastereomers (see ESI† for experimental details of the X-ray structures).[57]

efficiency of the underlying resolution (*in casu* the magnitude of the solubility difference of the diastereomers) is less important.

Conclusion

In conclusion, a novel strategy for the synthesis of enantiopure P-chiral phosphine oxides has been developed based on an unprecedented radical-mediated dynamic resolution. It provides the final piece for a practical and scalable approach to the preparation of P-chiral phosphines. In a subsequent asymmetric transformation, *tert*-butyl(hydroxyalkyl)phenylphosphine oxides are prepared in high yield and excellent stereoselectivity. Containing both P- and C-chirality, these are promising ligands and organocatalysts, all the more so because all four (quasi)-diastereomers were shown to be accessible.

Experimental

Dynamic resolution 1

(−)-(*R*,*R*)-Dibenzoyltartaric acid (590 mg, 1.65 mmol) and *tert*-butyl(phenyl)phosphine oxide (250 mg, 1.37 mmol) were dissolved at 50 °C in diisopropyl ether (DIPE, 20 mL). Subsequently, iodine (5 mg, 0.020 mmol) was added. The initially pale yellow mixture bleached within min and a white precipitate was formed. The mixture was stirred for 16 h at 69 °C, after which

the hot suspension was filtered. The white solid was dissolved in 1 M NaOH and $CHCl_3$ (10 mL each). The aqueous layer was separated and extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were dried (phase separator filter paper or $MgSO_4$) and the solvent was removed under reduced pressure to give (*R*)-*tert*-butyl(phenyl)phosphine oxide (230 mg, 1.32 mmol, 92% yield, 96% ee). Recrystallization from 1 : 1 toluene/DIPE gave >99% ee, 89% yield.

Asymmetric transformation 2

(*R*)-*tert*-Butyl(phenyl)phosphine oxide (100 mg, 0.55 mmol) was dissolved in 0.05 M aqueous NaOH (5 mL) at RT and the corresponding aldehyde (0.66 mmol, 1.2 equiv.) was added to form a white precipitate within several minutes of vigorous stirring. The slurry was heated at the indicated temperature for 16 h. After cooling down, the mixture was filtered and the residue washed with water (5 mL) and MTBE (5 mL) to afford the corresponding enantiopure and diastereomerically enriched *tert*-butyl(hydroxyalkyl)phenylphosphine oxide.

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